STN- Structure Search
11/19/07

10/599,473

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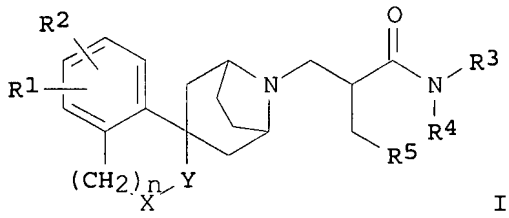
L4 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1338287 CAPLUS
DOCUMENT NUMBER: 146:81847
TITLE: α-(Aryl-or heteroaryl-methyl)-β-piperidino propanamide compounds as ORL1-receptor antagonists and their preparation, pharmaceutical compositions, and use in the treatment of CNS diseases
INVENTOR(S): Hashizume, Yoshinobu; Hirota, Masako; Koike, Hiroki; Matsumoto, Yukari; Mihara, Sachiko; Nakamura, Hiroshi
PATENT ASSIGNEE(S): Pfizer Japan Inc., Japan; Pfizer Inc.
SOURCE: PCT Int. Appl., 45pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006134486	A2	20061221	WO 2006-IB1642	20060609
WO 2006134486	A3	20070222		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2005-691939P P 20050617
OTHER SOURCE(S): MARPAT 146:81847
GI



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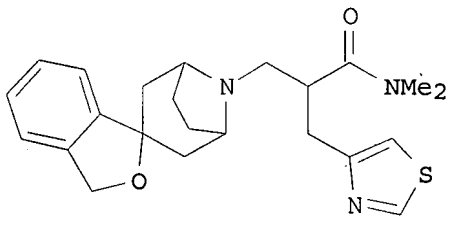


II

AB This invention provides the compds. of formula I, or a pharmaceutically acceptable salt thereof. Compds. of formula I wherein R1 and R2 are independently H, halo, and C1-3 alkyl; R3 and R4 are independently H,

(un)substituted C3-6 cycloalkyl, and (un)substituted C1-3 alkyl; R5 is (un)substituted (hetero)aryl; -X-Y- is CH2O, CH(CH3)O, and C(CH3)2O; and n represents 0, 1 and 2; and their pharmaceutically acceptable salts thereof, are claimed. These compds. have ORL1 -receptor antagonist activity; and therefore, are useful to treat diseases or conditions such as pain, various CNS diseases etc. Example compound II was prepared by bromination of 4-methylthiazole; the resulting 4-(bromomethyl)-1,3-thiazole underwent addition to tert-Bu diethylphosphonoacetate to give tert-Bu 2-(diethoxyphosphoryl)-3-(1,3-thiazol-4-yl)propanoate, which underwent elimination to give tert-Bu 2-(1,3-thiazol-4-ylmethyl)acrylate, which underwent conjugate addition of 3'H-spiro[8-azabicyclo[3.2.1]octane-3,1'-[2]benzofuran] to give tert-Bu 3-(3'H,8H-spiro[8-azabicyclo[3.2.1]octane-3,1'-[2]benzofuran]-8-yl)-2-(1,3-thiazol-4-ylmethyl)propanoate, which underwent hydrolysis to give the corresponding propanoic acid TFA salt, which underwent condensation with dimethylamine hydrochloride to give compound II. All the invention compds. were evaluated for their ORL1 receptor antagonistic activity. From the assay, it was determined that compound II exhibited a Ki value of 1.8 nM.

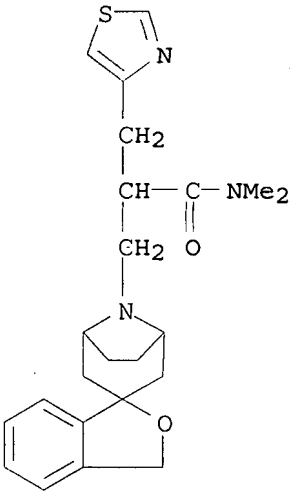
IT 917395-01-8P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(drug candidate and intermediate; preparation of α-aryl-β-piperidino propanamide compds. as ORL1-receptor antagonists useful in treatment and prevention of CNS diseases)

RN 917395-01-8 CAPLUS

CN Spiro[8-azabicyclo[3.2.1]octane-3,1'(3'H)-isobenzofuran]-8-propanamide, N,N-dimethyl-α-(4-thiazolylmethyl)- (CA INDEX NAME)



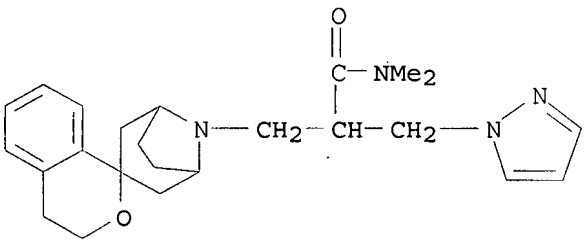
IT 917395-02-9P 917395-04-1P 917395-06-3P
917395-08-5P 917395-10-9P 917395-12-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

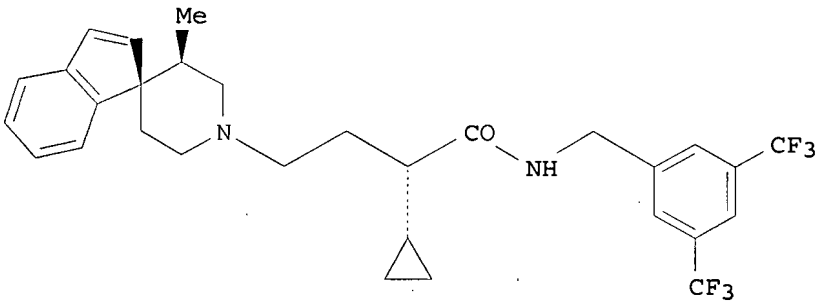
(drug candidate; preparation of α-aryl-β-piperidino propanamide compds. as ORL1-receptor antagonists useful in treatment and prevention of CNS diseases)

RN 917395-02-9 CAPLUS

CN Spiro[8-azabicyclo[3.2.1]octane-3,1'(3'H)-isobenzofuran]-8-propanamide, N,N-dimethyl-α-(4-thiazolylmethyl)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (CA INDEX NAME)



L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:830241 CAPLUS
DOCUMENT NUMBER: 145:327676
TITLE: 4-Amino-2-alkyl-butyramides as small molecule CCR2 antagonists with favorable pharmacokinetic properties
AUTHOR(S): Butora, Gabor; Morriello, Gregori J.; Kothandaraman, Shankaran; Guiadeen, Deodialsingh; Pasternak, Alexander; Parsons, William H.; MacCoss, Malcolm; Vicario, Pasquale P.; Cascieri, Margaret A.; Yang, Lihu
CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2006), 16(18), 4715-4722
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



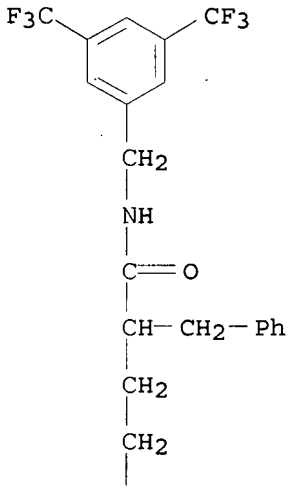
I

AB A systematic examination of the central aromatic portion of the lead (2S)-N-[3,5-bis(trifluoromethyl)benzyl]-2-(4-fluorophenyl)-4-(1'H-spiro[indene-1,4'-piperidin]-1'-yl)butanamide (9) led to the discovery of a novel class of CCR2 receptor antagonists, which carry small alicyclic groups such as cyclopropyl, cylobutyl, or cyclopropylmethyl attached at C2 of the carbon backbone. The most potent compound discovered, namely (2S)-N-[3,5-bis(trifluoromethyl)benzyl]-2-cyclopropyl-4-[(1R,3'R)-3'-methyl-1'H-spiro[indene-1,4'-piperidin]-1'-yl]butanamide (I), showed very high binding affinity (IC50 = 4 nM, human monocyte) and excellent selectivity toward other related chemokine receptors. The excellent pharmacokinetic profile of this new lead compound allows for extensive in vivo evaluation.

IT 691874-50-7P 691874-66-5P 909717-73-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino alkyl butyramides as CCR2 antagonists with favorable pharmacokinetic properties)

RN 691874-50-7 CAPLUS
CN Spiro[1H-indene-1,4'-piperidine]-1'-butanamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-α-(phenylmethyl)- (CA INDEX NAME)

PAGE 1-A



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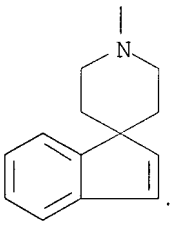
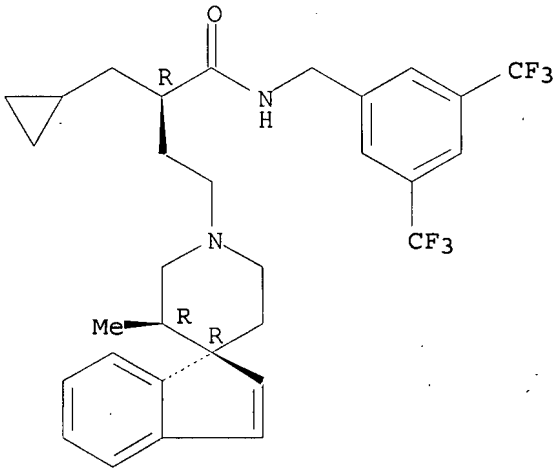


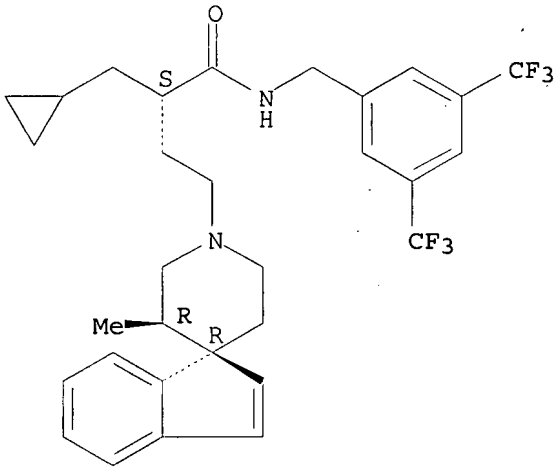
RN 691874-66-5 CAPLUS
CN Spiro[1H-indene-1,4'-piperidine]-1'-butanamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-α-(cyclopropylmethyl)-3'-methyl-, (αR,1R,3'R)- (CA INDEX NAME)

Absolute stereochemistry.



RN 909717-73-3 CAPLUS
CN Spiro[1H-indene-1,4'-piperidine]-1'-butanamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-α-(cyclopropylmethyl)-3'-methyl-, (αS,1R,3'R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Inventor

L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1075775 CAPLUS
DOCUMENT NUMBER: 143:367215
TITLE: Preparation of α-(hetero)arylmethyl-β-piperidinopropanamides as ORL1-receptor antagonists
INVENTOR(S): Hirota, Masako; Mihara, Sachiko; Nakamura, Hiroshi; Koike, Hiroki; Matsumoto, Yukari
PATENT ASSIGNEE(S): Pfizer Japan Inc., Japan; Hashizume, Yoshinobu; Pfizer Inc.
SOURCE: PCT Int. Appl., 272 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2005092858	A2	20051006	WO 2005-IB751		20050316
WO 2005092858	A3	20060302			
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2561488	A1	20051006	CA 2005-2561488		20050316
EP 1732893	A2	20061220	EP 2005-718251		20050316
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BR 2005009307	A	20070904	BR 2005-9307		20050316
JP 2007530656	T	20071101	JP 2007-505650		20050316
NL 1028624	A1	20051003	NL 2005-1028624		20050324
NL 1028624	C2	20060221			
US 2005277659	A1	20051215	US 2005-92503		20050329
US 7279486	B2	20071009			
MX 2006PA11265	A	20061215	MX 2006-PA11265		20060929
US 2007197500	A1	20070823	US 2006-599473		20060929
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			WO 2005-IB751	W	20050316

OTHER SOURCE(S): MARPAT 143:367215

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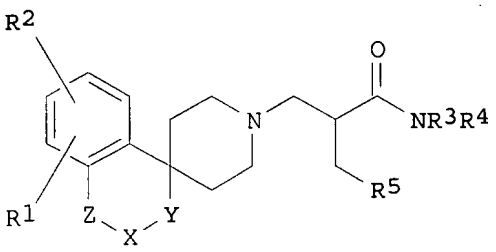

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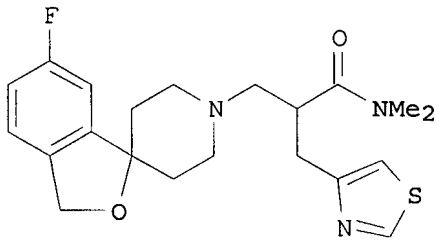
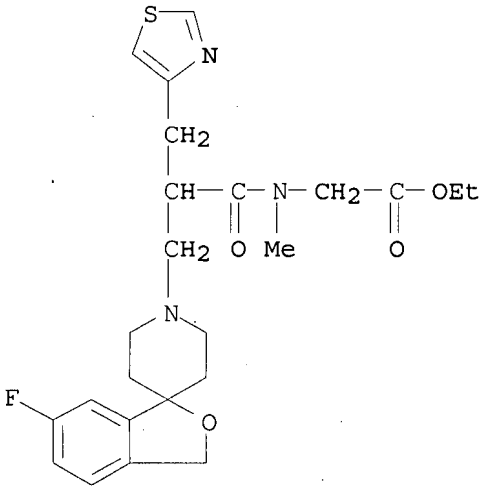
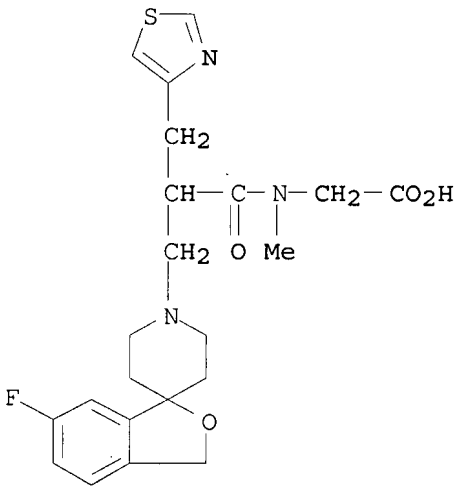


II

AB Title compds. I [R1-2 = independently H, halo, alkyl; R3 = H, cyclo/alkyl, tetrahydrofuranyl, etc.; R4 = H, alkyl, or NR3R4 = (un)substituted pyrrolidin-1-yl, piperidin-1-yl, pyrazin-1-yl, etc.; R5 = (un)substituted



RN 866224-52-4 CAPLUS
CN Glycine, N-[2-[(6-fluorospiro[isobenzofuran-1(3H),4'-piperidin]-1'-yl)methyl]-1-oxo-3-(4-thiazolyl)propyl]-N-methyl- (9CI) (CA INDEX NAME)



L4 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:412814 CAPLUS
DOCUMENT NUMBER: 140:423589
TITLE: Preparation of piperidinylbutyramides and related compounds as modulators of CCR-2 chemokine receptor activity
INVENTOR(S): Butora, Gabor; Pasternak, Alexander; Yang, Lihu; Zhou, Changyou
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 239 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2004041279 A1 20040521 WO 2003-US34009 20031024
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AU 2003284984 A1 20040607 AU 2003-284984 20031024
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US 2005261325 A1 20051124 US 2005-528329 20050318
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WO 2003-US34009 W 20031024
OTHER SOURCE(S): MARPAT 140:423589

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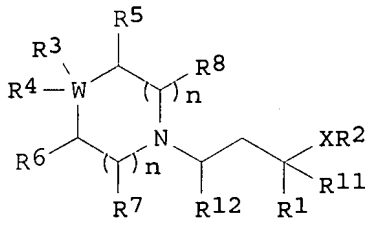

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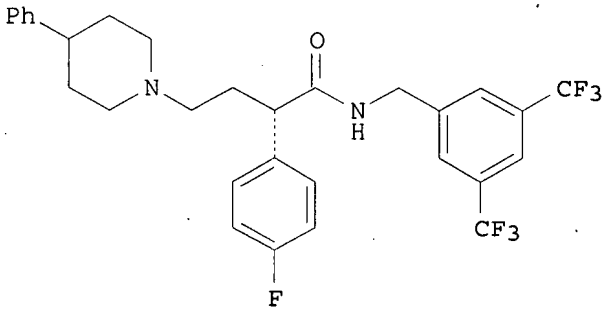


II

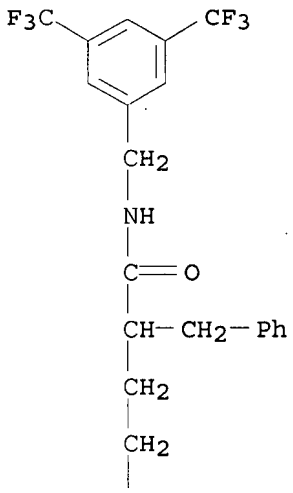
AB Title compds. [I; W = C, N, O; X = NR10, O, CH2O, CONR10, CO2, etc.; R10 = H, (substituted) alkyl, Ph, PhCH2, alkyl, cycloalkyl; R1 = H, (substituted) alkyl-Y-Ph, alkyl-Y-heterocyclyl, etc.; Y = bond, O, S, SO, SO2, NR10; R2 = (substituted) alkylphenyl, alkylheterocyclyl; R3 = H, (substituted) alkylphenyl, alkylheterocyclyl, CF3, cycloalkyl, etc.; R4 = H, OH, alkyl, alkoxy, cyano, etc.; R3R4 = atoms to form (substituted) indene, benzofuran, isobenzofuran, benzothiofuran, isobenzofuran rings; R5-R8 = H, OH, alkyl, alkoxy, O, halo, CF3, CO2R9, etc.; R9 = H, (substituted) alkyl, cycloalkyl, Ph, PhCH2; R3R5, R4R6, R5R6, R7R8 = atoms to form (substituted) rings; R11 = H, halo, alkyl, OH, alkoxy, NR9R10, etc.; R12 = H, alkyl, CO2R9; n = 0-3], were prepared Thus, title compound (II) was prepared by reaction of 4-phenylpiperidine with the corresponding aldehyde in the presence of Na(OAc)3BH. I bound to CCR-2 receptor with IC50 ≤1 μM.

IT 691874-50-7P 691874-52-9P 691874-66-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reparation of piperidinylbutyramides and related compds. as modulators of CCR-2 chemokine receptor activity)

RN 691874-50-7 CAPLUS
CN Spiro[1H-indene-1,4'-piperidine]-1'-butanamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-α-(phenylmethyl)- (CA INDEX NAME)

PAGE 1-A



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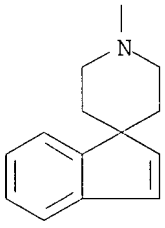
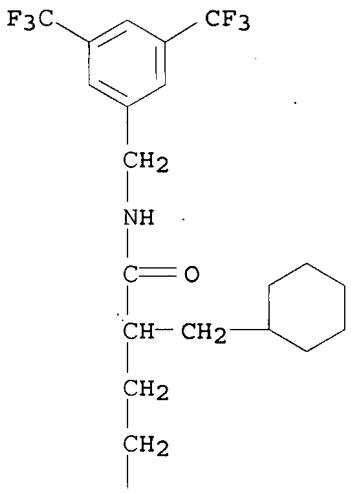


RN 691874-52-9 CAPLUS
CN Spiro[1H-indene-1,4'-piperidine]-1'-butanamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-α-(cyclohexylmethyl)- (CA INDEX NAME)

PAGE 1-A



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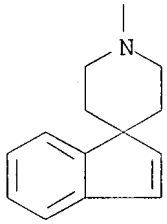
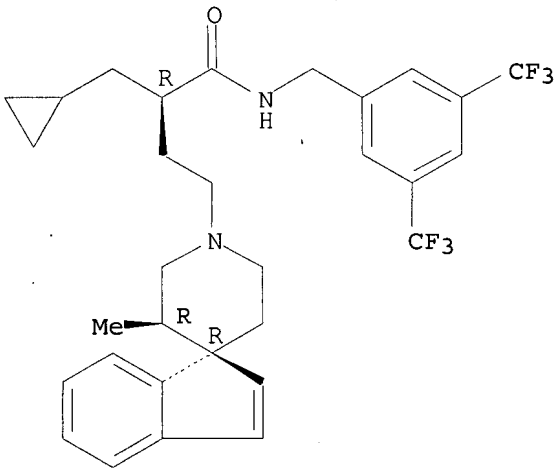


RN 691874-66-5 CAPLUS
CN Spiro[1H-indene-1,4'-piperidine]-1'-butanamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-α-(cyclopropylmethyl)-3'-methyl-, (αR,1R,3'R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L3          340 S L1 FULL

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L4            4 S L3

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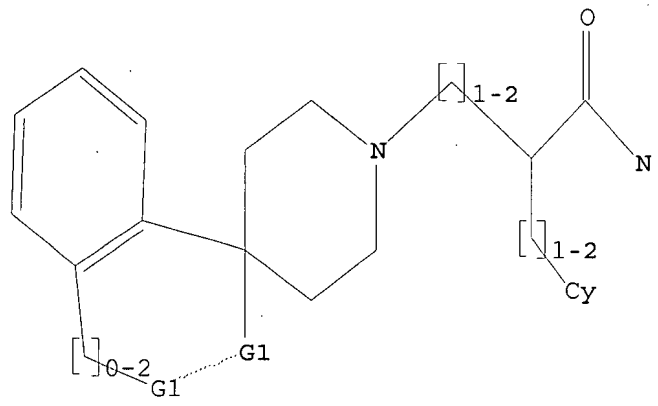

G1 C,O,S,N

Structure attributes must be viewed using STN Express query preparation.

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